



Treating bladder adenocarcinoma

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Introduction

Urothelial carcinoma is the sixth most common malignancy in the US with estimated 81,190 new cases and 17,240 deaths respectively for 2018. The prognosis of bladder cancer remains poor and worsens when tumor becomes muscle invasive (1). Transitional cell carcinoma is the most common bladder cancer histology, accounting for more than 90%, whereas other histologies account for no more than 2–3% per variant (2). Consequently, the most robust data exist for the most common subtype, that has resulted not only into established guidelines (3,4) but also to a great amount of research and to the approval of 5 new agents the previous years (5). On the other hand, adenocarcinoma of the bladder is a very rare entity, accounting for less than 2% of cases (6), with no randomized trials and no established treatment algorithms for this histology. As a result, therapeutic decisions are usually based on retrospective data. Therefore, studies such the recently published study by Facundo, Davaro *et al.* at *World Journal of Urology* (7) are very interesting and clinically meaningful. Davaro *et al.* studied retrospective data from 851 pure adenocarcinoma patients from the National Cancer Database, with muscle invasive disease comparing different treatment modalities; surgery *vs.* radiotherapy *vs.* combination *vs.* no treatment (7).

Prognosis

In concordance with transitional cell carcinoma, factors that were found to be associated with worse survival for

adenocarcinoma bladder cancer patients were: increased age, T status, lymph node involvement and metastasis. In this study, the importance of treatment centralization in high volume centers, was once again highlighted, especially for rare histologies, since, it was correlated with decreased risk for mortality.

Chemotherapy

The role of chemotherapy in the treatment of non-metastatic muscle invasive bladder cancer of transitional cell histology is well established. Specifically in the neoadjuvant setting (8), it has been associated with a 8% benefit in 5-year survival in a meta-analysis of 3,285 patients (9) and represents a universally accepted standard in current guidelines (3,4).

On the other hand, in the absence of high-level evidence for adenocarcinomas of the bladder, the role of chemotherapy for local disease, remains debatable (6,10). Neoadjuvant chemotherapy was found to decrease the frequency of non-organ-confined disease without prolonging overall survival in a subpopulation of 357 adenocarcinomas out of 2018 non-TCC bladder cancers studied retrospectively by Vetterlein *et al.* (11). Unfortunately, Davaro *et al.* reported no results regarding chemotherapy and this could be considered a clear disadvantage of the study. Chemotherapy, either perioperative or at disease relapse, could be a confounding factor of the comparison of different treatment modalities.

In addition, this is one of the largest to date retrospective studies of purely bladder adenocarcinomas and due to this limitation, a chance for useful information regarding the role of chemotherapy in this rare bladder cancer entity has been missed (7).

Cystectomy

Radical cystectomy is the cornerstone of local TCC of the bladder, while combined chemoradiotherapy remains a valuable option for those patients that are either unfit or unwilling to undergo cystectomy (3,4). The role of surgery for bladder adenocarcinomas has been evaluated with two different approaches. Firstly, Lughezzani *et al.* and Ghoneim *et al.* studied the role of cystectomy in a mixed histology population and compared its efficacy between the different histologies of bladder cancer. Adenocarcinomas were found to equally benefit from cystectomy as cancer specific mortality-free rates were not statistically different between adenocarcinomas and TCCs (12,13). Davaro *et al.* added value to cystectomy for bladder adenocarcinomas studying the same subject from a different prospective; comparing the different treatment modalities in a pure adenocarcinoma population. At this study cystectomy was found to be the only treatment that independently contributed to a reduction in the overall mortality (7).

External beam radiotherapy (EBRT)

EBRT alone is not a preferable treatment option for bladder cancer patient as it is considered inferior to radical cystectomy (14). Nevertheless, the addition of chemotherapy improves outcomes and chemoradiation can be used as a radical treatment alternative for patients with local disease that are either unfit or unwilling to undergo cystectomy (15). Although the same strategy is intuitively followed for bladder adenocarcinomas, this is rather extrapolated from TCC guidelines and is not supported by strong evidence. Until now Zaghoul *et al.* had reported a possibly positive effect on the adjuvant setting through best local disease control (16). Davaro *et al.*'s study adds further information and questions the role of XRT to the treatment of bladder adenocarcinomas: EBRT alone was not found to offer any survival benefit and the EBRT and surgery combination lost its statistical significance when metastatic disease was excluded from the analysis (7). Interestingly, median 2 and 5 years OS in the EBRT arm was found lower than the no treatment arm.

No treatment

One of the very interesting findings of the study published in the *World Journal of Urology* is that the majority of the patients had not undergone the radical treatment that is considered the standard of care (7) and additionally some of them had not undergone any treatment at all. Although in our opinion this is mostly a result of the absence of experience as well as clear recommendations for this rare entity, another fact that may explain this attitude is the frequent poor performance status of these patients at diagnosis, which was associated with a higher incidence of 30 and 90 days' mortality. Again, missing information about chemotherapy utilization make the detailed evaluation of outcomes in this population difficult.

Conclusions

In view of the absence of level I evidence, this study provides the strongest possible evidence that radical cystectomy should be considered the standard of care for localized bladder adenocarcinomas. This modality is the only radical treatment to date, that has been proven to prolong survival in this and previous studies. The role of neoadjuvant chemotherapy and EBRT remains questionable and further data should be analyzed before these two therapies could be considered standard practice. It is of utmost importance that patients with this rare histology should be treated in high volume centers.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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